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10/628,783	07/25/2003	Martin Friedlander	TSRI-900.1	5526

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EXAMINER

NGUYEN, QUANG

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 03/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

10/628,783

**Applicant(s)**

FRIEDLANDER ET AL.

**Examiner**

Quang Nguyen, Ph.D.

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 17 December 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-65 is/are pending in the application.
- 4a) Of the above claim(s) 1-49 and 62-65 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 50-61 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Claims 1-65 are pending in the present application.

Applicants' election without traverse the invention of Group II (Claims 50-61) in the Response filed on 12/17/04 is acknowledged.

Claims 1-49 and 62-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/17/04.

Accordingly, claims 50-61 are examined on the merits herein.

### ***Claim Objections***

Claims 50 and 55 are objected to because they are dependent on non-elected claims 1 and 49, respectively. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

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which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 55-57 are directed to a method of inhibiting retinal angiogenesis in the eye of a patient in need of retinal angiogenesis inhibition comprising intravitreally injecting a transfected lineage negative hematopoietic stem cell population including endothelial progenitor cells. Claims 58-61 are drawn to a method of delivering transgenes to the retinal vasculature of a patient comprising intravitreally injecting a transfected lineage negative hematopoietic stem cell population derived from bone marrow into the eye of the patient, wherein the stem cell population has been transfected with a therapeutically useful gene, including a gene that is useful for inhibiting retinal neovascularization.

Relevant to the nature of the elected invention, the specification teaches by exemplification showing the transfection of cells in a mouse Lin<sup>-</sup> bone marrow hematopoietic stem cell population containing a population of endothelial precursor cells with a DNA encoding a potent angiostatic fragment of Tryptophanyl-tRNA synthetase (T2-TrpRS). When the T2-TrpRS transfected Lin<sup>-</sup> HSC composition was intravitreally

injected into mouse eyes, the primary retinal vascular network had significant abnormalities and the formation of the deep retinal vacuature was nearly completely inhibited 10 days post-injection. In contrast, retinas of mouse eyes injected with a control-plasmid transfected Lin<sup>-</sup> HSC composition had normal primary and secondary retinal vascular plexuses (see pages 24-26, and Table 2).

The above evidence has been noted and considered. When read in light of the specification, the intended sole purpose for the methods as claimed is to attain therapeutic effects for ocular treatments (see specification, page 1, lines 15-18; and Summary of the Invention). However, the instant specification is not enabled for the instant broadly claimed invention for the following reasons.

**1. *The breadth of the claims***

The claims are drawn to a method of inhibiting retinal angiogenesis in the eye of a patient in need of retinal angiogenesis inhibition or a method of delivering transgenes to the retinal vasculature of any patient, said method comprises intravitreally injecting a transfected lineage negative hematopoietic stem cell population obtained from any bone marrow sources (e.g., xenogeneic, allogeneic as well as autologous) into the eye of the patient, and wherein the stem cell population has been transfected with any therapeutically useful gene, including a gene that is useful for inhibiting retinal neovascularization.

**2. *The state and the unpredictability of the prior art***

The nature of the instant claims falls within the realm of cell-based gene therapy art. At about the effective filing date of the present application (7/25/2002), the

attainment of any therapeutic effects via gene therapy (*in vivo* or *ex vivo*) was and continues to be unpredictable as evidenced at least by the teachings of Smith, L.E.H. (Nature Medicine 8:932-934, 2002) and McFarland et al. (Expert Opin. Biol. Ther. 4:1053-1058, 2004). In reviewing the same set of data presented in the present application, a skilled artisan Smith still states "The use of stem cells as drug delivery vehicles **has the potential** to selectively and potently deliver drugs to the back of the eye in physiologically meaningful doses. As this is where most vision threatening pathologies occur, the use of these cells-as trophic cellular devices or drug delivery vehicles-**holds great promise** for millions of patients suffering from currently untreatable diseases" (page 934, last paragraph of column 2 continues to first paragraph of column 3); "Will angiostatic transformed **cells function in models of hypoxia-induced pathological retinal neovascularization as well as in the developmental model? Will HSCs function in other models of pathological vessel loss in the retina such as in diabetes or retinopathy of prematurity?**" (page 934, bottom of column 1 continues to top of column 2); and "Another potentially troubling possibility is that non-hematopoietic stem cells could incorporate into the retina and **develop into tumors. It is unclear what the long-term effects are of a heterologous group of stem cells in the retina**" (bottom of the middle paragraph in column 2 on page 934). Even in 2004, with respect to the issue of gene therapy for proliferative ocular diseases McFarland et al. still summarize the state of the art in the following statement, "Proliferative ocular disease accompanied by neovascularisation result in vision loss for millions of people each year. Although traditional surgical

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treatment is always destructive and often inefficacious, **gene therapy has the potential** to regulate, reverse and prevent these diseases through biological, rather than mechanical approaches. **The choice of which system to use in order to deliver a particular gene is still being elucidated**....Antiproliferative gene delivery holds considerable promise for the future of ocular therapeutics as those diseases are remarkably prevalent and morbid. One gene therapy trial is underway to treat patients with AMD; many more will certainly follow" (page 1056, col. 2, second paragraph).

### ***3. The amount of direction or guidance provided***

Apart from the exemplification showing that upon intravitreal injection of T2-TrpRS transfected Lin<sup>-</sup> HSC composition into mouse eyes, the primary retinal vascular network had significant abnormalities and the formation of the deep retinal vaculature was nearly completely inhibited 10 days post-injection, the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain any therapeutic effects as a result of intravitreally injecting a bone marrow, lineage negative hematopoietic stem stem cell population transfected with T2-TrpRS gene into a patient, let alone for any therapeutically useful gene. How can the attainment of significant abnormalities in primary and secondary retinal vascular plexuses in mice treated with T2-TrpRS transfected Lin<sup>-</sup> HSC composition be correlated with any therapeutic effects contemplated by Applicants? It is also uncertain how the expression of the anti-angiogenic peptide T2-TrpRS, or any other useful therapeutic gene products, is turned off when it is no longer needed without adversely affecting the structure and functionality of the eyes in the treated patients. Nor is it clear whether angiostatic transformed cells

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can function in models of hypoxia-induced pathological retinal neovascularization or in other models of pathological vessel loss in the retina such as in diabetes or retinopathy of prematurity as noted by Smith, L.E.H. Since the prior art at the effective filing date of the present application fails to provide such guidance, it is incumbent upon the present disclosure to do so. It is interesting to further note that based essentially on the same set of data, some of Applicants state that **"The vascular rescue seen in this model is substantial, but it is not clear what effect, if any, Lin<sup>+</sup> HSC treatment would have on the neuroretinal degeneration typically associated with these disorders"** (Otani et al., Nature Medicine 8:1004-1010, 2002; page 1009, col. 2, bottom of first paragraph).

The physiological art is recognized as unpredictable (MPEP 2164.03). Given the state of the prior art as already discussed above, coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to **make and use** the methods as claimed.

Furthermore, the instant disclosure also fails to provide sufficient guidance for a skilled artisan on to overcome the adverse host immune responses against injected xenogeneic or allogeneic transfected hematopoietic stem cell population of the present invention. It is uncertain whether the xenogeneic and/or allogeneic transfected hematopoietic stem cell populations can withstand the adverse host immune reactions for a sufficient period of time in the retinal vasculature of the treated patient to yield the desired therapeutic effects contemplated by Applicants. Once again, given the lack of sufficient guidance provided by the present application it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

***4. The quantity of experimentation provided***

The instant specification fails to provide any example indicating that any therapeutic effect contemplated by Applicants has been attained as a result of intravitreally injecting a bone-marrow, lineage negative hematopoietic stem cell population transfected with any therapeutically useful gene, including a gene that inhibits retinal neovascularization in any patient.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the relevant cell-based gene therapy in ocular diseases art for the attainment of therapeutic effects, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **make and use** the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55-57 and 59-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 55, it is unclear what is encompassed by the phrase "a transfected stem cell population according to claim 49". This is because claim 49 has not recited any transfected stem cell population. Accordingly, the metes and bounds of the claim are not clearly determined. Clarification is requested.

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Claims 56-57 and 59-60 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is the transfecting step for a population of lineage negative hematopoietic stem cells including endothelial progenitor cells in order to obtain the transfected lineage negative hematopoietic stem cell population.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 50 is rejected under 35 U.S.C. 102(e) as being anticipated by Wilson et al (US Patent 6,767,737).

The claim is drawn to a transfected lineage negative hematopoietic stem cell population comprising a bone marrow-derived lineage negative hematopoietic stem cell population containing endothelial progenitor cells in which at least about 50% of the cells include the cell markers CD31 and c-kit, transfected with a gene encoding a therapeutically useful peptide.

Wilson et al disclose the preparation of a CD34+ FGFR+ cell population having a "primitive phenotype" which also expresses c-kit marker (52% of cells) and CD31 (70% of cells) from human bone marrow, cord blood, general circulation or embryonic cells (see abstract; col. 3, lines 55-62; col. 6, lines 33-59; Figure 1; and examples). Wilson et al further teach that the isolated primitive stem cell population contains endothelial and/or stromal stem cells (see Summary of the invention). Additionally, Wilson et al teach that the stem cells can be used to target the delivery of angiostatic agents and anti-tumor agents to the rapidly proliferating vascular bed associated with tumors (col. 9, lines 7-15) or genetically engineered to secrete proteins such as t-PA, clotting factors or adenosine deaminase (col. 9, lines 26-59).

Accordingly, the transfected or genetically engineered primitive stem cell population of Wilson et al. meets every limitation of the instant claim. Therefore, the reference anticipates the instant claim.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 50-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al (US Patent 6,767,737) in view of Schimmel et al. (US 2003/0017564 with the effective filing date of 2/23/2001) .

Wilson et al disclose the preparation of a CD34+ FGFR+ cell population having a "primitive phenotype" which also expresses c-kit marker (52% of cells) and CD31 (70% of cells) from human bone marrow, cord blood, general circulation or embryonic cells (see abstract; col. 3, lines 55-62; col. 6, lines 33-59; Figure 1; and examples). Wilson et al further teach that the isolated primitive stem cell population contains endothelial and/or stromal stem cells (see Summary of the invention). Additionally, Wilson et al teach that the stem cells can be used to target the delivery of angiostatic agents and anti-tumor agents to the rapidly proliferating vascular bed associated with tumors (col. 9, lines 7-15) or genetically engineered to secrete proteins such as t-PA, clotting factors or adenosine deaminase (col. 9, lines 26-59).

However, Wilson et al. do not specifically teach that their stem cell population is transfected with a gene encoding a therapeutically useful peptide which is an anti-angiogenic peptide or an anti-angiogenic protein fragment, even though they disclosed that the stem cells can be used to target the delivery of angiostatic agents and anti-

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tumor agents to the rapidly proliferating vascular bed associated with tumors (col. 9, lines 7-15).

However at the effective filing date of the present application, Schimmel et al already disclose that truncated Tryptophanyl-tRNA synthetase (TrpRS) polypeptides, e.g., mini TrpRS, T1 and T2) are potent polypeptides for the inhibition of angiogenesis (Figures 1, 3, 4 and examples), as well as recombinant expression vectors encoding the same (see Summary of the invention, page 2, col. 2). Schimmel et al further teach that cells can be transfected *in vivo*, *ex vivo* or *in vitro* with their recombinant vectors, and following *ex vivo* or *in vitro* transfection, the cells can be implanted into a host (page 11, paragraph 0121). Schimmel et al also teach that angiostatic trpRs therapy can be used to oppose the angiogenic activity of endogenous and exogenous angiogenic factors, and to prevent further growth or even regress solid tumors, since angiogenesis and neovascularization are essential steps in solid tumor growth (page 12, paragraph 0132).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the teachings of Wilson et al. by genetically modifying their stem cell population with recombinant expression vectors encoding truncated fragments of TrpRS to target these potent angiostatic peptides to the rapidly proliferating vascular bed associated with tumors to inhibit the growth of solid tumors in light of the teachings of Schimmel et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the truncated fragments of TrpRS have been demonstrated by Schimmel et al. to be potent angiostatic peptides, and that they are also specifically taught to be used to oppose the angiogenic activity of endogenous and exogenous

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angiogenic factors, and to prevent further growth or even regress solid tumors by *in vivo* and *ex vivo* gene approaches.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Wilson et al., Schimmel et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

### **Conclusions**

#### ***No claims are allowed.***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

**To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300.**

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

*Quang Nguyen, Ph.D.*

A handwritten signature in black ink, appearing to read 'Quang Nguyen', with a stylized flourish at the end.